CARCINOGEN RISK ASSESSMENT GUIDELINES
CHARGE FOR THE SAB REVIEW
July 27-28, 1999

BACKGROUND

In September 1986, EPA published *Guidelines for Carcinogen Risk Assessment* (51 *Federal Register* 33992-34003). Since that time, significant gains have been made in understanding the carcinogenic process while the Agency's experience with the 1986 Guidelines has revealed several limitations in their approach to cancer risk assessment. In April 1996, EPA proposed revisions to the 1986 Guidelines (61 *Federal Register* 17960-18011). These revisions are the result of a number of EPA-sponsored meetings, e.g., a 1994 peer review workshop (*Report on the Workshop on Cancer Risk Assessment Issues*, EPA/630/R-94/005a), recommendations contained in the National Academy of Sciences (NAS) 1994 report *Science and Judgment in Risk Assessment,* and extensive EPA and federal reviews.

The intent of the revised Guidelines is to take into account the available knowledge about the carcinogenic process and to provide flexibility for the future in assessing data, recognizing that the Guidelines cannot always anticipate future research findings. Compared to the 1986 Guidelines, the revised Guidelines emphasize a more complete evaluation of all relevant information and provide more guidance on the use of information on the way an agent produces cancer (mode of action). The emphasis on mode of action is to help reduce the uncertainties associated with assessing and characterizing human cancer risk and to help identify whether there is special concern for particular subpopulations, e.g., children. The revised Guidelines recognize a variety of conditions under which the cancer hazard may be expressed (e.g., route or magnitude of exposure to the agent).

The revised Guidelines retain the Agency's traditional use of a linear low dose extrapolation as a default procedure to quantify possible human cancer risks. However, the Guidelines recognize that different modes of action for carcinogenicity (e.g., direct action with DNA, hormonal or other growth-signaling processes) are being elucidated as the scientific understanding of the carcinogenic processes advances. The Agency will increasingly need to assess mechanistic studies that have implications for hazard, dose-response, and risk characterization.

In February 1997, the SAB reviewed the Proposed Guidelines and generally commended (EPA-SAB-EHC-97-010) the Agency for its efforts to incorporate new scientific information and for being responsive to recommendations from authoritative groups, e.g., the NAS and the Presidential/Congressional Commission on Risk Assessment and Risk Management (GPO #55-000-00568-1, 1997).

On January 20-21, 1999 at the request of the Agency, the SAB reviewed selective sections of the 1996 Proposed Guidelines that were revised to address SAB and public recommendations dealing with hazard descriptors, the use of mode of action information, dose-response analysis, and the approach to the use of margin of exposure analysis. A draft report (EPA-SAB-EC-99-0XX) from the January review has recently been made available. In their report the SAB recommends that the Agency finalize the Guidelines now to consolidate the progress made to date. One outstanding issue from the SAB reviews is the recommendation to expand the discussion in the Guidelines regarding special subpopulations, particularly children. The Agency is now requesting the SAB's review of revised sections of the Guidelines that address children's risk. The review document[1] contains highlighted text throughout the document that is intended to raise the awareness of risk assessors to the issue of children as a special subpopulation. Where appropriate, guidance is provided and risk assessors are directed to Agency methods and data sources that are useful in conducting assessments for children. The Agency envisions that the revised cancer guidelines will be used in concert with the Agency's existing risk assessment guidelines addressing mutagenicity, development toxicity, reproductive toxicity, neurotoxicity, chemical mixtures, and exposure. All of these guidelines will be consulted when conducting risk assessments to ensure that information from studies on carcinogenesis and other health effects is considered together in an overall characterization of risks to children. From time to time, EPA revises its risk assessment guidelines to reflect advances in the science or methodologies and also produces supplementary guidance that expands more fully on issues touched upon in the guidelines, e.g., guidance on the assessment of renal tumors in male rats (EPA, 1991), guidance on the assessment of thyroid follicular cell tumors (EPA 1998), and guidance on conducting probabilistic risk assessments (EPA, 1998). EPA intends to continue with this practice and supplement the revised cancer guidelines through peer consultation workshops and peer reviewed guidance. Areas that will receive particular emphasis include: how to better inform and improve the assessment of children's risk, inter-individual variability in toxicokinetic and toxicodynamic capacity, and methodologies for margin of exposure analysis and other dose-response approaches.

Charge Questions

1. The Agency is now seeking the Science Advisory Board's review of the highlighted revisions to the draft sections that provide guidance on incorporating relevant data into the evaluation of carcinogenic risk to subpopulations, in particular children. The Guidelines also provide pointers to additional existing Agency guidance on assessing risk to children. Some of these key supplementary documents (or relevant excerpts) are being provided as background.

2. The Agency seeks the Science Advisory Board's review of the soundness of certain default science policy positions as they relate to assessing risk in the absence of agent-specific data. In particular as addressed in the draft preamble:

A. A linear default approach is used when the mode of action information is supportive of linearity or, alternatively, when the information is insufficient to describe a mode of action. As described in the 1986 Guidelines, a linear default approach using the linearized multi-stage

procedure is generally thought to produce an upper bound on potential risk at low doses that adequately accounts for human variability. Based on our preliminary analysis, the straight line approach described in the draft revised guidelines gives numerical results about the same as a linearized multistage procedure. Given the current state of knowledge, the draft guidelines assume that the upper bound of the linear default procedure adequately accounts for variability unless there is case-specific information for a given agent that indicates a particularly sensitive subpopulation. Does the SAB agree that this default position is appropriate.

B. The Mode of Action Framework provides for analysis of all data to evaluate a postulated mode of action and its relevance to humans including subpopulations of concern. When sufficient information is developed to show a mode of action for a specific tumor type in mature animals and is determined to be relevant to humans, an evaluation will be made as to whether this mode of action is qualitatively applicable to children, i.e., same sequence of key events is involved. Ideally, we would have data pertinent to the question with respect to the agent under assessment. In the absence of such data, a cogent biological rationale needs to be developed regarding whether the mode of action producing tumors in the adults is applicable to children. Please comment on the considerations, as outlined in the draft guidelines, that would constitute the basis for concluding that the mode of action is applicable to children. Do the case studies for chemicals T and Z in Appendix D provide useful illustrative examples?

C. When application of the Framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a nonlinear mode of action, a margin of exposure approach is taken. Given the considerations that need to be addressed in the Framework (including the applicability of the mode of action to children), does the SAB agree with the view that a separate factor to protect children, in addition to the usual factor for human variability, is not necessary in the margin of exposure?

3. The Guidelines (Chapter 3) provide default approaches for converting a human equivalent dose for adults into a human equivalent dose for children for oral and inhalation exposures. Are these default approaches reasonable, in light of what is known about doses to children, the information that will typically be available to the risk assessor, and the Agency's policy of erring on the side of children's health when information is not available?

4. The Guidelines provide an example (Appendix F) of how slope factors can be adjusted in lifetime and partial lifetime exposure scenarios to reflect data on early-life sensitivity. Is this approach appropriate?

5.. In a letter to Administrator Browner, dated May 12, 1999, the Children’s Health Protection Advisory Committee (CHPAC) suggested a series of questions that should be considered by the Science Advisory Board in reviewing the draft revisions to the Guidelines. The Agency has prepared responses to the questions posed in the CHPAC letter. The Science Advisory Board is asked to comment on the Agency’s responses.

1.The current document constitutes work in progress. It incorporates some changes to the January 1999 review draft based on discussions at the January meeting and the recently released draft letter from the Science Advisory Board (SAB), dated May 27, 1999. The Agency is continuing to address the SAB recommendations. However, for the purpose of providing a context for a discussion of the guidance on assessing children's risk, the Agency has provided the most current version of the draft guidelines.

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